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PATENT

Harry
Mar. 10, 01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Goelet et al.

Examiner: Arthur, L.

Serial No.: 09/258,132

Group Art Unit: 1655

Filed: February 26, 1999

Docket No.: 13017-3

For: Nucleic Acid Typing by Polymerase Extension Of Oligonucleotides Using Terminator Mixtures

Kalow & Springut LLP
488 Madison Avenue, 19th Floor
New York, NY 10022

February 28, 2001

Assistant Commissioner for Patents
Washington, DC 20231

AMENDMENT AND REPLY TO OFFICE ACTION

Sir:

This amendment is a reply to the Office Action mailed on August 31, 2000 in the above-identified application. In view of the remarks and amendments provided hereinbelow, reconsideration is respectfully requested. The time set for filing a reply to the Office Action expires on November 30, 2000. Pursuant to a petition for a three-month extension of time filed concurrently with this reply, the period set to reply to the outstanding Office Action expires on February 28, 2001 and therefore this amendment and reply are timely filed.

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2/28/01
Date

J. Colwell
Name

Please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claims 60 and 63 as follows:

60. (Amended) A method of determining the identity of one or more nucleotide bases at specific positions of one or more nucleic acid molecules of interest, comprising:

(a) treating a sample comprising one or more nucleic acid molecules of interest, if the nucleic acid molecules of interest comprise double-stranded nucleic acid, so as to obtain unpaired nucleotide bases spanning the specific positions, or directly employing step (b) if the nucleic acid molecule of interest are single-stranded;

(b) contacting the sample from step (a) with one or more unique oligonucleotide primers, wherein;

(i) each unique oligonucleotide primer hybridizes, under high stringency hybridization conditions, to a different stretch of nucleotide bases present in the nucleic acid molecules of interest which is immediately adjacent to the nucleotide base to be identified with that unique oligonucleotide primer, so as to form a duplex such that the nucleotide base to be identified is the first unpaired base of the nucleic acid molecule of interest immediately downstream of the 3' end of the oligonucleotide primer, and

(ii) each unique oligonucleotide primer has a unique affinity moiety which permits affinity separation of the oligonucleotide primer from all the other oligonucleotide primers and wherein the affinity moiety specifically binds to a discrete position on a solid support, such discrete position is specific for the affinity moiety of the oligonucleotide primer;

(c) contacting the duplexes from step (b), in the absence of dATP, dCTP, dGTP, or dTTP, with four different terminators, each terminator comprising a different detectable label, of a nucleic acid template-dependent primer extension reaction, wherein one of the terminators is complementary to the nucleotide base to be identified by each of the oligonucleotide primers, wherein the contacting is under conditions sufficient to permit a template-dependent primer extension reaction which incorporates the complementary terminator onto the 3' end of each of the unique oligonucleotide primers to thereby extend the 3' end of each of the unique oligonucleotide primers by one terminator; [and]

(d) contacting the sample from step (c) with the solid support; and

[(d)] (e) determining the presence and identity of the nucleotide base at the specific position or positions in each nucleic acid molecule of interest by detecting at each position of the solid support the detectable marker of the terminator incorporated at the 3' end of each of the unique oligonucleotide primers, such that each nucleotide base to be identified can be individually identified by detecting at each position of the solid support the detectable marker of the terminator incorporated at the 3' end of each unique oligonucleotide primer.

63. (Amended) A method of analyzing the sequence of nucleic acid molecules of interest, comprising:

(a) attaching a plurality of affinity moieties, wherein the affinity moiety comprises a unique sequence of nucleotides, to a solid support at defined positions;

(b) hybridizing the nucleic acid molecules of interest in solution to a plurality of oligonucleotide primers which comprise sequences of nucleotides complementary to the affinity moiety of step (a), under hybridization conditions, to generate a duplex;

(c) subjecting the hybridized primers to a template mediated single base primer extension reaction which comprises providing to the hybridized primers four terminators corresponding to each of the four nucleotide bases, to extend the hybridized primers by the addition of a terminator;

(d) sorting the extended primers by affinity capture by the affinity moieties of step (a);

(e) observing the identity and location of the terminators and thus determining the base at each of a plurality of sites of interest for the nucleic acid molecules of interest.

REMARKS

Claim 60 has been amended to make clearer the step of binding of the unique oligonucleotides to the solid support via unique affinity moieties present on each of the unique

oligonucleotides. Support for this amendment can be found at page 31, lines 23-30. Claim 63 has been amended to correct clerical errors. No new matter has been added.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 60 –63 as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. The Examiner contends that the specification does not support primers bound to discrete positions on solid supports, a plurality of unique oligonucleotides primers attached to a solid support, primer extension of immobilized primers or sorting extended primers by affinity capture. The Examiner particular objects to the use of the term "discrete positions."

Applicants respectfully disagree. Clear support for all of these concepts and the implementation of these concepts can be found throughout the specification. For example, the specification at page 31 lines 23-35 provides the following language (with emphasis added in bold).

> By specifically tagging the oligonucleotide primer(s), or template(s) with a moiety that does not effect the 3' extension reaction yet permits affinity separation, the extension product(s) can be separated post-reaction from the unincorporated terminators, other components of the reagents, and/or the template strand. **Several oligonucleotides can be analyzed per extension reaction if more than one affinity agent is used.**
>
> In principle, the combination of four differently labeled terminators and **many primers** or templates **tagged with different groups** permits the typing of many **different** nucleic acid sequences simultaneously.

Taken together, these paragraphs make clear that the inventors were in possession of the concepts that the Examiner contends are not supported by the specification. Support for binding of oligonucleotide primers to discrete positions or defined positions necessarily follows from the above cited language because the analysis of different nucleic acid sequences by using primers or

templates tagged with different groups implies that the primers or templates bind to discrete or defined positions on a solid support. There is clear support from the above cited language for having oligonucleotide primers bind through the interaction of different affinity groups, such as complementary nucleic acid sequences, in such a way that **different** nucleic acids can be analyzed simultaneously. Different affinity groups that bind to the groups or sequences on the primers and allow for the typing of many different nucleic acid sequences simultaneously implies that the primers are bound to discrete or defined positions on a solid support. One skilled in the art would also recognize from the above cited language that the inventors intended the concept of sorting the extended primers by affinity capture as in claim 63.

It is therefore respectfully requested that this rejection be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 60-63 have been rejected under 35 U.S.C.§112, second paragraph. The examiner has taken the position the claims are indefinite because of the recitation of the terms "discrete position" and "defined positions." The Examiner contends that it is unclear from these claims "whether the primer or affinity moiety is attached at a specific and unique position on a solid support or whether a discrete position includes a spot in a dot blot, for example, as shown in figure 8..." Office Action at page 4.

Applicants respectfully disagree that there is any lack of clarity in these claims. Each of the claims recite either "discrete positions on a solid support" (claims 60-61) or "solid support at defined positions" (claim 63). The claims clearly indicate the binding to discrete or defined positions on a solid support. Dot blots are one example of a solid support. Solid supports also find support in other places in the specification, for example at page 27, lines 12-24.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections under the judicially created doctrine of obviousness-type double patenting

Claims 60-63 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 13-56 of U.S. Patent No. 6,004,744. Claims 60-63 have also been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 5,888,819 in view of Dattagupta et al. (EP 0 297 379). Claims 60-63 have also been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-59 of copending application No. 09/258,132 in view of Dattagupta et al.

Applicants disagree with these rejections, but in order to expedite prosecution, Applicants submit a Terminal Disclaimer for claims 60-63. Applicants respectfully request reconsideration and withdrawal of this rejection.

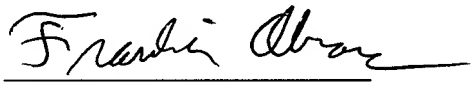
Conclusion:

In view of the foregoing amendments to the claims, and the remarks set forth above, reconsideration and allowance are respectfully solicited.

Other than the three-month extension of time fee and fee for the terminal disclaimer, no other fees are believed to be necessary. If any additional fee is determined to be necessary, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 11-0171.

If there are any questions or comments relating to the present application, the Examiner is respectfully invited to contact Applicants' attorney at the telephone number set forth below.

Respectfully submitted,



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